Specialty Conference

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Refer to: O'Rourke RA, Crawford MH, Johnson AD, et al: Prolapsing mitral valve leaflet syndrome—University of California, San Diego (Specialty Conference). West J Med 122:217-231, Mar 1975

Prolapsing Mitral Valve Leaflet Syndrome

DR. ROBERT A. O'ROURKE:* *Midsystolic clicks and late systolic murmurs, previously thought to be innocent and extracardiac or pericardial in origin,[1-6] have recently been shown to be a part of a common and highly variable clinical syndrome caused by a functional abnormality of the mitral valve.[7-12] Since 1961 when Reid attributed both the midsystolic click and the late systolic murmur to mitral valve regurgitation,[13] there has been considerable information obtained concerning the clinical, echocardiographic, cineangiographic and pathologic findings in this syndrome. Recent data indicate that prolapse of the mitral valve leaflets, variously called the click-murmur syndrome, the billowing mitral valve leaflet syndrome and the floppy valve syndrome, may occur in as much as 5 to 10 percent of the population.[14-16] Dr. Michael Crawford will begin this specialty conference by discussing the clinical presentation of patients with mitral valve prolapse.*

DR. MICHAEL H. CRAWFORD:† The clinical presentation of the prolapsing mitral valve leaflet syndrome is quite diverse and except for a preponderance of women, the typical patient cannot be stereotyped. The variability of the clinical findings in these patients is related to the underlying causes, to the extent of the mitral valve abnormality and to other unidentified physiologic factors. The following discussion will describe the symptoms and signs of the prolapsing mitral valve leaflet syndrome and their underlying physiologic mechanisms.

Most of the patients with mitral valve prolapse are probably asymptomatic and clinical findings are detected by auscultation during a physical examination for other reasons. Most of the reported patients in the literature, however, had one or more symptoms which might have been caused by the mitral valve abnormality. The most common complaints are palpitation, chest pain, dyspnea and fatigue. The frequently vague nature of these and other complaints has provoked some to consider them functional or psychoneurotic symptoms.[10]

The symptom of palpitation associated with the prolapsed mitral valve syndrome is clearly related to the presence of arrhythmias. Frequent atrial and ventricular premature beats, paroxysmal supraventricular tachyarrhythmias and ventricular tachycardia have been reported in patients with this syndrome.[17] Arrhythmias are occasionally present on the resting electrocardiogram (ECG), but more often can be induced or aggravated by physical exertion. However, the presence of ar-

This work was supported in part by Graduate Training Grant HL 05846.

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rhythmias during exercise is not related to the presence of ischemic (ST-T wave) ECG changes.[18]

Despite the frequency of arrhythmias detected in these patients, syncope is an unusual complaint. However, the increased incidence of sudden death reported by some authors in patients with the familial form of this syndrome has been attributed to arrhythmias,[19] and the overall reported incidence of sudden death in the literature has been estimated to be 1.2 percent.[17] Therefore, some authors recommend routine exercise testing of all persons with this syndrome to detect dangerous arrhythmias.[20]

The chest pain associated with this syndrome is particularly difficult to evaluate. Although it may be substernal, it is often prolonged and poorly related to exertion. It rarely resembles typical angina pectoris, but it can be incapacitating. Ischemic ECG changes have been reported at rest and during exercise but they do not correlate with the presence or the absence of chest pain.[18] Recent work at our institution has shown that the chest pain in this syndrome can be reproduced by selectively elevating systemic arterial pressure and hence left ventricular systolic pressure with intravenously administered phenylephrine.[21] The increased left ventricular systolic pressure would exert more force on the billowing mitral valve leaflets and increase papillary muscle tension during systole. If the increased tension in the papillary muscles interfered with regional blood supply or augumented regional oxygen demands excessively or both, pain could be produced. However, there is currently no documentation of abnormal levels of systemic arterial pressure in ambulatory patients with spontaneous pain. Thus, the precise mechanism of the chest pain in this syndrome remains speculative and it must be distinguished from the chest pain of ischemic heart disease.

Complaints of dyspnea and fatigue are common but are usually not progressive and are not associated with signs of congestive heart failure. Some patients describe typical episodes of hyperventilation. Objective evaluation of these complaints has shown no consistent reduction in exercise tolerance.[17]

The most common physical finding in this syndrome is the midsystolic click. The click is a high-pitched sound sometimes described as snapping or popping, which can vary considerably in intensity and timing from beat to beat. A single midsystolic click is the most common finding, but two, three or four are not unusual. Most often they occur 0.14 seconds or more after the first heart sound and if there are two or more clicks, they are usually .02 to .04 seconds apart. The clicks are thought to be generated by the sudden tensing of the mitral valve apparatus when the prolapsing mitral leaflet reaches its maximum posterior excursion.[8] They are best heard at the apex and lower sternal border near the mitral valve. Such high frequency midsystolic sounds have also been described in patients with pneumothorax, left ventricular aneurysms or aneurysms of the interventricular septum.[1,22] Midsystolic clicks must also be differentiated from systolic ejection sounds which arise from the semilunar valves or great vessels. Ejection sounds are best heard at the base of the heart, occur early in systole, are almost always single and usually do not vary appreciably in timing—as mentioned later.

The midsystolic click is often followed by a high-pitched late systolic murmur, which usually is heard best at the apex with the patient in the left lateral decubitus position. It is caused by blood regurgitating through the prolapsed mitral valve leaflet into the left atrium. The murmur is crescendo-decrescendo, peaking at the time of maximum mitral valve leaflet prolapse in late systole. Sometimes the murmur begins before the click and occasionally extends through the aortic component of the second sound.[23] The timing of the murmur is variable, and in some patients it is the only physical finding in this syndrome. When this

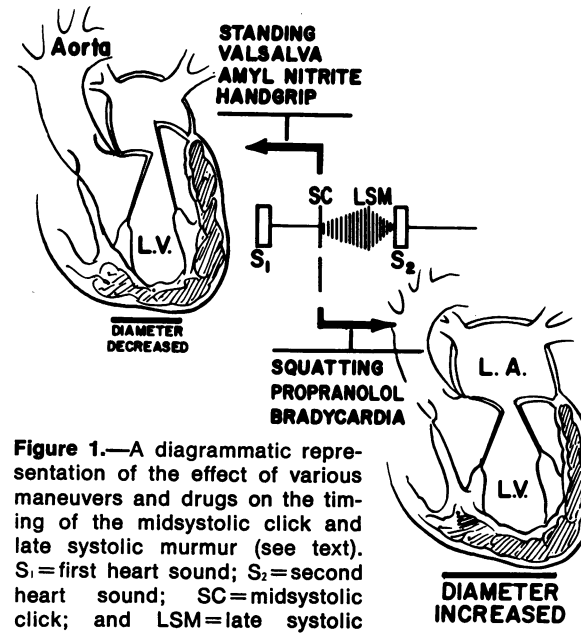

Figure 1.—A diagrammatic representation of the effect of various maneuvers and drugs on the timing of the midsystolic click and late systolic murmur (see text). S_1 = first heart sound; S_2 = second heart sound; SC = midsystolic click; and LSM = late systolic murmur.

occurs it must be distinguished from other systolic murmurs, especially those that peak late in systole, such as the murmur of papillary muscle dysfunction.

The midsystolic click and late systolic murmur associated with prolapse of one or both mitral valve leaflets are best identified by their characteristic responses to various maneuvers (Figure 1). Interventions which decrease left ventricular end-diastolic volume exaggerate chordal redundancy and increase the propensity for mitral leaflet prolapse. Therefore, prolapse occurs earlier in systole and the click and murmur move toward the first heart sound. The simplest way to decrease end-diastolic volume in the ambulatory patient is to have the subject sit or stand. Other methods include the Valsalva maneuver, amyl nitrate inhalation or increasing the heart rate with mild, submaximal handgrip exercise. With these provocative maneuvers, the murmur may become holosystolic and the click may move closer to the first sound, often disappearing within it or resembling an early systolic ejection sound. Conversely, interventions which increase left ventricular end-diastolic volume diminish the propensity for the mitral valve leaflets to prolapse and the click-murmur complex moves later in systole and may even disappear if prolapse is abolished. The easiest bedside maneuver to increase end-diastolic volume is rapid squatting which augments venous return to the heart, increases systemic peripheral resistance by compressing the femoral arteries and causes reflex bradycardia. Any intervention that slows the heart rate, such as the administration of the beta-adrenergic blocking drug propranolol, also will increase left ventricular end-diastolic volume. Thus, the end-diastolic left ventricular volume seems to be a major determinant of the onset of mitral valve prolapse and hence, the timing of the systolic click and murmur.

The intensity of the click is dependent on systolic left ventricular pressure and contractile force. Hence, with the Valsalva maneuver it becomes softer and with handgrip exercise it becomes louder. The intensity of the murmur varies with different maneuvers as does classical mitral regurgitation. Interventions which increase the intensity of the murmur, such as handgrip exercise, may also cause a honking or musical sound to occur during the murmur.[24] The response to amyl nitrate inhalation is usually biphasic. During the initial phase of vasodilatation after amyl nitrate inhalation, the murmur becomes softer, as does the murmur of rheumatic mitral regurgitation. Later, however, as reflex tachycardia develops, the murmur of mitral valve prolapse often increases as end-diastolic volume diminishes.

Certain variations in the findings described above tend to occur in patients with identifiable underlying heart diseases. The clicks described in some patients with rheumatic heart disease are lower pitched and do not change their timing predictably with the maneuvers outlined above. Also, the mitral regurgitant murmurs are more often pansystolic and frequently there are signs of associated mitral stenosis.[25] The clicks in patients with predominant ischemic heart disease can also be lower pitched. They seem to move appropriately with changes in ventricular volume but lack the spontaneous variation in timing seen in most patients with the prolapsed mitral leaflet syndrome.[26]

Other physical findings occur in these patients which may be related to the causes of the syndrome. Many patients without overt features of the Marfan syndrome have been found to have certain bony abnormalities, such as high-arched palate and chest and thoracic spine deformities.[27] Particular care should be taken to exclude associated atrial septal defect which has been reported to occur with increased frequency in patients with mitral valve prolapse. However, a late systolic click may mimic fixed splitting of the second heart sound and lead to the false impression of atrial septal defect.

The systolic murmur of mitral valve prolapse can usually be distinguished from other systolic murmurs by its response to the maneuvers described above. Idiopathic hypertrophic subaortic stenosis (IHSS), however, presents an especially challenging differential diagnosis. The systolic murmur due to left ventricular outflow obstruction resembles the murmur of mitral leaflet prolapse in many of its features and midsystolic clicks have occasionally been observed in patients with IHSS.[28] The murmur of IHSS may peak late in systole and it decreases in intensity and duration with squatting and increases with standing. However, isometric handgrip exercise usually decreases the intensity of the murmur of IHSS and the Valsalva maneuver *greatly* increases it, in contrast to the murmur of mitral leaflet prolapse. Also there is no early decrease in intensity of the murmur of IHSS with amyl nitrate inhalation as occurs with the murmur of mitral valve prolapse. However, the most consistent difference in the murmurs of mitral valve prolapse and IHSS is the

change in intensity that occurs in the cardiac cycle following a premature contraction, the murmur of subaortic stenosis increasing in duration and loudness and the murmur due to billowing mitral leaflets diminishing or remaining unchanged.

There is some evidence from the physical findings that the degree of mitral valve apparatus involvement may be progressive. Isolated clicks are more common in children, the complex of click and late systolic murmur is common in young adults and older patients tend to have prominent mitral regurgitant murmurs.[29] Several postulates have been entertained to explain this progression. One is that in many of these patients, subacute bacterial endocarditis develops which further impairs the valvular apparatus leading to more prominent mitral regurgitation. Another explanation is that the cumulative stress to the mitral apparatus resulting from initial chordal redundancy leads to further abnormalities in the structure of the mitral leaflets and even the adjacent ventricular wall (mitral regurgitation begets mitral regurgitation). Furthermore, rupture of the chordae tendineae, in the absence of endocarditis, occurs in patients with the prolapsed mitral valve leaflet syndrome.[30] However, the true incidence of progression of this lesion from mild mitral valve prolapse to severe mitral regurgitation is not well defined.

Findings on the electrocardiogram and vectorcardiogram have been reported to be abnormal in a high percentage of patients with the prolapsing mitral valve leaflet syndrome, even if patients with obvious coronary artery disease are excluded.[31] The most common finding is T-wave inversion in the inferior leads (II, III, AVF) and occasionally V_5 and V_6 (Figure 2). Rarely, Q waves and ST segment elevation are seen in these same leads.[32] Large "U" waves in the limb leads and a prolonged QT interval have also been reported. The arrhythmias seen in this syndrome do not seem to be related to these ECG abnormalities.[18,20] Various causes for these ECG abnormalities have been postulated such as (1) ischemia of the left ventricular wall adjacent to the papillary muscles that are under increased tension, (2) hyperventilation, (3) compression of the circumflex coronary artery by the billowing posterior leaflet and (4) the existence of a cardiomyopathy. However, these theories are unproven and the mechanism of the ECG abnormalities and arrhythmias remains obscure, as does the reason why they are seen only in some patients.

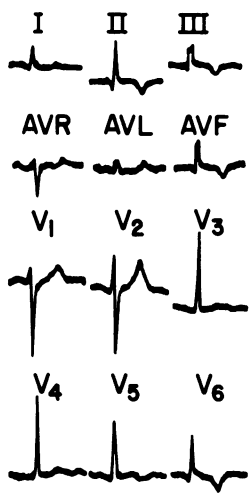

Figure 2.—Schematic representation of an electrocardiogram pattern seen in patients with the prolapsing mitral valve leaflet syndrome.

The variable clinical presentation of the prolapsing mitral valve leaflet syndrome can mimic many other cardiac diseases and make diagnosis difficult. Usually, the history, physical examination and electrocardiogram are sufficient, but some patients will require further procedures (discussed later) to confirm or exclude the diagnosis. Patients with a history of palpitation, syncope or sudden death in the family and those in whom arrhythmias are noted on physical examination or resting ECG should have an exercise ECG test.

DR. O'ROURKE: *The prolapsing mitral valve leaflet syndrome has been observed in association with a variety of clinical disorders including the Marfan syndrome, other connective tissue diseases, coronary artery disease and atrial septal defects. It often occurs in several members of the same family. As just described, the clinical manifestations of mitral valve disease are quite variable, with there being only an isolated systolic click in some patients and evidence of severe mitral regurgitation in others. Dr. Allen Johnson will discuss the structural abnormalities of the mitral valve and its supporting structures in patients with mitral valve prolapse and the possible causes of this syndrome.*

DR. ALLEN D. JOHNSON:* The phenomenon of prolapsing mitral valve leaflets, having been recognized only relatively recently, now encompasses a number of causes and pathophysiologic mechanisms. Originally felt to represent sounds of extra-

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TABLE 1.—*Pathophysiologic Mechanisms of Mitral Leaflet Prolapse*

1.	Mitral Leaflet Abnormalities
	(a) Excessive or redundant leaflet tissue
	(b) Myxomatous degeneration
2.	Chordae tendinae abnormalities
	(a) Shortened, fibrotic
	(b) Elongated, redundant
	(c) Ruptured
3.	Papillary muscle disorders
	(a) Abnormal orientation
	(b) Inadequate shortening
4.	Abnormalities of left ventricular contraction
	(a) Localized
	(b) Diffuse
5.	Abnormal function of the mitral annulus

cardiac origin, the characteristic clicks and murmurs identified with this syndrome have now been associated with various forms of dysfunction of the mitral valve apparatus. As reviewed by Perloff and Roberts,[33] the functional anatomy of the mitral valve includes: the left atrium, the mitral valve annulus, the mitral leaflets, the chordae tendinae, the papillary muscles and the left ventricular wall—particularly the regions of insertion of the papillary muscles. Disordered anatomy or function of any of these structures may cause the mitral valve to function abnormally, resulting in mitral regurgitation. Conceptually, abnormal function of any portion of the mitral apparatus might permit excessive posterior excursion of the mitral valve leaflet(s) during systole, and it is no surprise, therefore, that the prolapsing mitral valve leaflet syndrome has been associated with abnormalities of each of the various structures mentioned.

While the definite diagnosis of prolapse of the mitral valve leaflet(s) requires anatomic documentation of a specific type of abnormal mitral valve motion by cineangiographic or echocardiographic techniques (as mentioned later), many of the clinical features are so typical as to suggest the proper diagnosis. Thus, as discussed by Dr. Crawford, the auscultatory findings of systolic clicks and systolic murmurs, a history of atypical chest pain, an abnormal resting electrocardiogram and recurrent arrhythmias encountered in this clinical syndrome often have as a common denominator angiographic or echocardiographic evidence of mitral valve leaflet prolapse.

In reviewing the various causes identified and mechanisms postulated as causes of the billowing mitral valve leaflet syndrome, each of the various elements of the mitral valve apparatus must be considered (Table 1). Excessive or redundant mitral leaflet tissue has been identified in a number of cases, and can involve the anterior leaflet or the posterior leaflet—or portions of either leaflet. Redundant leaflet tissue is commonly found to be involved with myxomatous degeneration and is a frequent finding in patients who have the typical features of the Marfan syndrome or of Erdheim's cystic medial necrosis.[34] However, myxomatous degeneration can be confined to the mitral valve leaflets without other clinical or pathologic manifestations of disease.[35,36] Various abnormalities of the chordae tendinae have been specifically identified in this syndrome. If chordae to either leaflet, or portions of a single leaflet, are unequally involved with a pathologic process, inadequate coaptation of the mitral leaflets during left ventricular systole might occur. In this regard, short, attenuated chordae as well as elongated, redundant chordae tendinae have been identified in the billowing mitral leaflet syndrome. Chordal fibrosis, as occurs in patients with rheumatic mitral disease, has been associated with myxomatous mitral valve leaflets.[8,35,37,38] In this regard, systolic clicks with late systolic murmurs have been described in patients with acute rheumatic fever. Thin, elongated chordae have been identified as well in patients with mitral valve prolapse; whether the decrease in thickness is a primary or secondary abnormality remains conjectural.[23,35,38] Frank rupture of chordae tendinae can also result in mitral leaflet prolapse.[38]

Dysfunction of the papillary muscles, particularly in the setting of coronary artery disease, has often been associated with auscultatory and angiographic evidence of mitral regurgitation. The systolic murmur in this setting is also unlike that of rheumatic mitral regurgitation since it is mid- or late systolic in timing. Recently, the clinical features associated with prolapse of the mitral valve leaflets have been described in patients with coronary artery disease, giving rise to the hypothesis that dysfunction of the papillary muscles can result in prolapse of the mitral valve leaflets during systole.[39] While systolic clicks or atypical mid to late systolic murmurs or both have been well-documented in patients with ischemic heart disease, angiographic evidence of mitral leaflet systolic prolapse in this setting is not frequent. Considering the relative frequency of each of these two disorders, ischemic heart disease and prolapse of the mitral leaflets, the existence of both dis-

orders in the same patient could represent a chance occurrence. In patients without evidence of coronary artery disease, in whom prolapse of the mitral leaflets has been shown, abnormal orientation or inadequate shortening of the papillary muscles has been identified, and could be responsible for the abnormal leaflet position during systole.

Abnormalities of left ventricular contraction have been described in patients with systolic clicks with or without evidence of associated billowing of the mitral valve leaflets. The contraction abnormalities described can be categorized as either localized or diffuse. Localized or regional disorders of the left ventricular contraction described in this syndrome include decreased systolic shortening of the inflow area of the left ventricle, increased or decreased contraction of the midportion of the left ventricle, shortening of the base to apex left ventricular axis, and diminished or exaggerated contraction of the posterior left ventricular wall.[40-44] It is unclear whether abnormal tension on the mitral valve leaflets, chordae tendinae and papillary muscles is responsible for the abnormal left ventricular contraction pattern, or whether the abnormal left ventricular contraction pattern alters the geometric relation of the papillary muscle and suspensory apparatus of the mitral valve leaflet—allowing it to prolapse with resulting mitral regurgitation.

Diffuse abnormalities of left ventricular function have also been described in patients with billowing mitral leaflets. Mitral valve prolapse has occasionally been noted in patients with hypertrophic obstructive cardiomyopathy, in whom the anterior mitral leaflet is displaced anteriorly during systole and the posterior leaflet sometimes prolapses into the left atrium.[45] In nonobstructive, hypertrophic cardiomyopathy, mitral leaflet prolapse has been documented, particularly when there is a pronounced decrease in left ventricular end-systolic volume.[45] As will be discussed later in this conference, Gulotta and associates have described diffusely abnormal left ventricular contraction patterns in some patients with billowing mitral valve leaflets.[46]

Abnormal function of the mitral annulus has also been suggested as a possible cause of mitral leaflet prolapse, and billowing of the mitral leaflets has been observed in patients with mitral annulus calcification and associated angiographic evidence of decreased systolic contraction of the mitral annulus.[47]

Patients with secundum atrial septal defects have a higher than expected incidence of mitral valve prolapse; the pathophysiologic explanation for this association is unclear, although mitral leaflet prolapse is only rarely noted in other forms of congenital heart disease.[48]

The familial incidence of systolic clicks and mid to late systolic murmurs has been noted since the original descriptions of this syndrome.[24,49,50] Whether the familial occurrence of billowing mitral valve leaflets includes some or all of the above postulated mechanisms is not certain at present.

DR. O'ROURKE: *As has been mentioned, the clinical presentation of patients with the prolapsing mitral valve leaflet syndrome is quite variable and this syndrome often occurs in association with other cardiac disorders. It would therefore be desirable to have a sensitive, accurate, noninvasive technique for evaluating patients with suspected mitral valve prolapse. Fortunately, echocardiography when properly done is a reliable method for diagnosing prolapse of one or both mitral valve leaflets. Dr. Robert Davidson will describe the ultrasound technique and echocardiographic findings in patients with this syndrome.*

DR. ROBERT M. DAVIDSON:* Echocardiography has become an increasingly important clinical tool in the diagnosis of a variety of cardiac disorders. There is no better example than that of mitral valve prolapse, in which an echocardiogram is frequently diagnostic of anterior or posterior mitral leaflet billowing into the left atrium. In order to understand the specific abnormality in this condition, it is useful to review the motion of the normal mitral valve echogram as illustrated in Figure 3. The anterior leaflet of the mitral valve is easily recorded and has a characteristic "M" shape. Various points on the echogram have been labeled A through F by convention and correspond to the position of this structure at specific times in the cardiac cycle. Following the onset of left ventricular diastole at Point D, the mitral valve opens and the anterior leaflet reaches its maximum anterior position at Point E. The mitral valve then partially closes and Point F is the end of partial closure. It then opens further with atrial contraction at Point A, and begins to close before the onset of left ventricular contraction which occurs at Point B. The valve is closed completely at Point C, and then

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during systole gradually moves anteriorly back to Point D. This anterior motion from C to D is probably due to emptying of the left ventricle during systole. It is this systolic portion of the mitral valve echo, the C to D segment, upon which the following discussion will be centered.

Depending upon the exact transducer position, various portions of the posterior mitral valve leaflet are also commonly detected. The movements of this leaflet are approximately opposite in direction to those of the anterior mitral valve leaflet during diastole. Shortly after the onset of systole (Point C) both leaflets come together and stay in apposition until Point D, at which time valve opening begins.

The abnormal echocardiographic appearance of the mitral valve in the syndrome of mitral valve prolapse was first recognized in 1970 by Shah and Gramiak who described two types of abnormal systolic motion.[51] In the first type, which has become recognized as most characteristic of this syndrome, the early systolic motion is normal, but there is an abrupt posterior displacement of one or both mitral valve leaflets in mid to late systole,

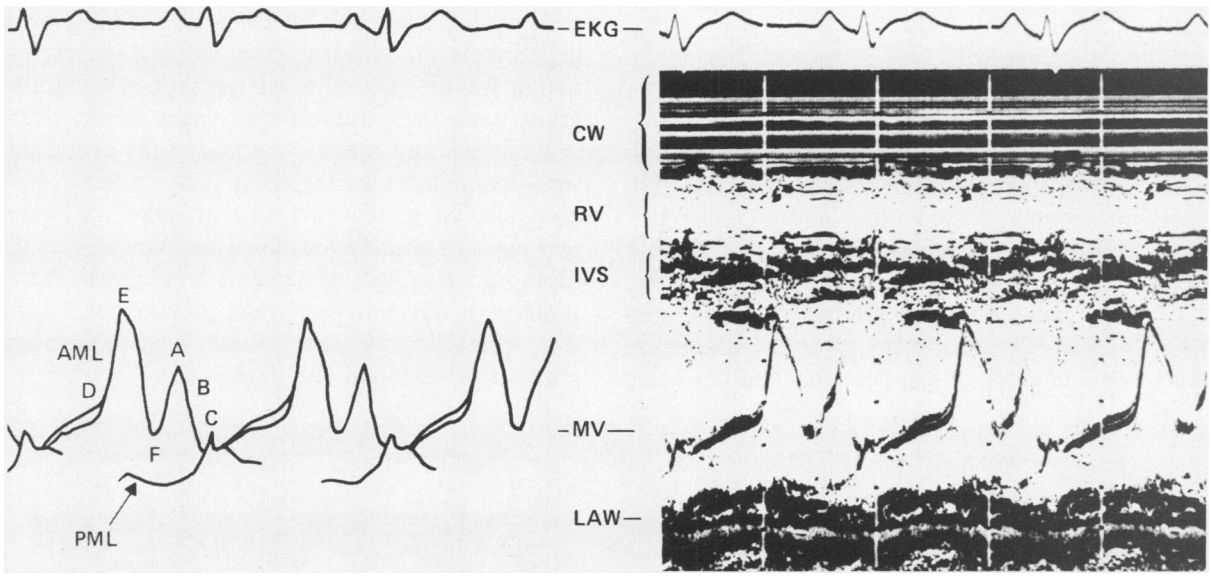

Figure 3.—Normal mitral valve echogram. The recorded echo is illustrated on the right and a schematic tracing of the mitral valve motion on the left. CW = chest wall; RV = right ventricle; IVS = interventricular septum; MV = mitral valve; AML = anterior mitral leaflet; PML = posterior mitral leaflet; and LAW = left atrial wall. The letters A through F correspond to the letters described in the text.

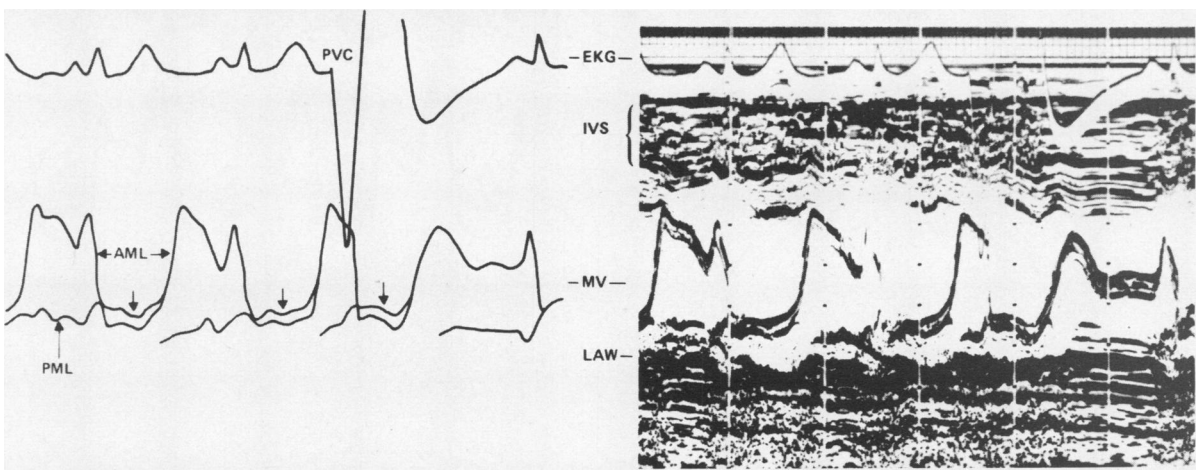

Figure 4.—Echocardiogram from a patient with mitral valve prolapse. The areas of posterior displacement of both mitral leaflets are illustrated by arrows. This abnormal motion is exaggerated following a premature ventricular contraction.

as illustrated in Figure 4. This ultrasound pattern is frequently observed in patients with a midsystolic click and late systolic murmur,[49-53] and has not been seen in any other condition. The onset of this posterior mitral leaflet displacement occurs very shortly after the systolic click,[52] and occurs earlier in systole and lasts longer when the subject is given amyl nitrate to inhale.[53] During the posterior displacement of the mitral leaflets, there is usually some separation between the anterior and posterior leaflets. Although this separation was initially felt to correlate with the presence and degree of mitral regurgitation, subsequent studies have not substantiated this hypothesis.[54,55]

Many patients with this syndrome, including patients with mitral valve prolapse who have atypical physical findings, have a second type of abnormal echocardiogram.[55] In these patients, the mitral valve echogram shows a gradual and smooth posterior motion of the mitral leaflets which begins shortly after the onset of systole and is followed by a gradual anterior motion back to the C Point (Figure 5). This gradual posterior and then anterior systolic motion gives the echogram a smooth hammock-like appearance and has been referred to as the pansystolic type of abnormality. In addition, there are frequently multiple *abnormally* moving parallel echoes recorded during systole in patients with mitral valve prolapse which are probably a result of the echo beam passing through the folds of a redundant mitral valve.[54,55] This finding is often seen in patients with mitral valve prolapse due to ruptured chordae tendineae,[56] as well as in patients with mitral valve prolapse and either a holosystolic murmur, multiple systolic clicks or no abnormal physical findings.[54,55] There is an overlap in physical findings between patients with the two main types of abnormal echocardiograms, and the echocardiographic pattern cannot be reliably predicted from the physical examination. The explanation for the two different types of echocardiograms seen in mitral valve prolapse is not clear at this time, and needs to be more fully evaluated with combined angiographic and echocardiographic studies. The absence of either of these two types of abnormal echocardiograms at rest or during interventions in patients with mitral valve prolapse is uncommon and the presence of a normal, carefully recorded mitral valve echogram makes this diagnosis less likely.

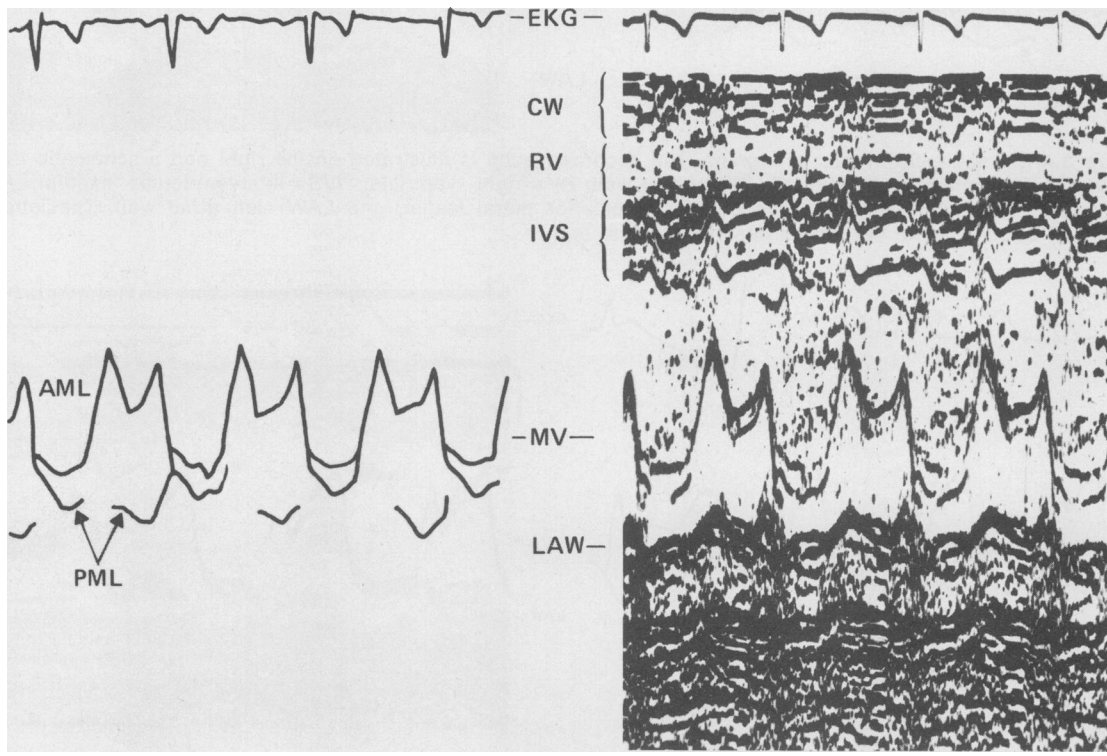

Figure 5—Pansystolic type of mitral valve prolapse. This shows the hammock or U-shaped abnormal type of systolic motion and two distinct separate echoes during systole, which represent the anterior and posterior leaflets.

Several precautions need to be taken, however, in obtaining and interpreting ultrasound recordings of the mitral valve in patients with suspected prolapse. Careful scanning of the mitral valve by tilting the transducer is necessary to identify this structure at all levels. Mitral valve prolapse should not be excluded unless this is done, and unless the posterior mitral valve leaflet is recorded. The best transducer angle for recording mitral valve prolapse is one in which the junction of the posterior left ventricular wall and posterior left atrial wall is seen behind the mitral valve echo.[57] When the posterior left ventricular wall, rather than the posterior left atrial wall, is recorded behind the mitral valve, the motion of the posterior mitral valve leaflet during systole is frequently obscured by the motion of the left ventricular wall. It is often desirable to place the transducer at an interspace lower than usual (fifth rather than fourth left intercostal space) and direct the transducer angle upward toward the left atrium to accomplish this.[59] Certain factors must be considered in order to avoid the incorrect ultrasound diagnosis of mitral valve prolapse. For example, a limited posterior motion of the mitral valve can be recorded at the beginning of systole in normal persons, lasting no more than 0.04 seconds.[54] This posterior displacement is small and is followed by a normal gradual anterior systolic motion, and should not be confused with the echo patterns seen in mitral valve prolapse.

Another normal finding which could be confused with mitral valve prolapse is the occasional recording of multiple mitral valve echoes during systole. These are parallel echoes which have *normal* anterior motion, are not widely separated, and are probably due to the ultrasound beam striking the mitral valve apparatus at an angle, thus passing through it at several points.[54] This multiplicity of echoes, however, is often exaggerated in mitral valve prolapse.

Another possible point of confusion is with an echocardiogram in idiopathic hypertrophic subaortic stenosis (IHSS), in which there is a characteristic abnormal systolic anterior motion of the mitral valve. Although this echo pattern consists of an initial exaggerated systolic motion of the anterior mitral valve leaflet followed by a posterior motion, the posterior motion in subaortic stenosis is anterior to the C Point while in mitral valve prolapse it is posterior to the C Point.[54] Moreover, amyl nitrate inhalation exaggerates the anterior motion in IHSS and exaggerates the posterior displacement in mitral valve prolapse.

Finally, in patients with low cardiac output there often are mitral valve echoes which show very little systolic anterior motion and can thus be confused with the pansystolic type of mitral valve echogram seen in the prolapsing mitral valve leaflet syndrome. However, in this type of echogram there is no posterior displacement of the mitral valve, only a limited amount of anterior motion.[54]

If these simple precautions are taken, echocardiography is extremely reliable in diagnosing mitral valve prolapse. Although the diagnosis can often be made on physical examination alone, physical findings can be variable, intermittent or absent in this syndrome and are less specific than the echocardiogram. Since patients with this syndrome are often symptomatic and are prone to complications, the echocardiogram provides a simple, safe and reliable method for making this important diagnosis.

DR. O'ROURKE: *Cardiac catheterization and left ventricular angiography are often unnecessary in patients with typical auscultatory and echocardiographic features of mitral valve prolapse. However, in some patients cardiac catheterization is necessary to evaluate the severity of the mitral valve regurgitation, the existence of left ventricular dysfunction, the presence or absence of coronary artery disease and the possibility of associated cardiac disease. Dr. Martin LeWinter will discuss the cardiac catheterization and angiographic findings in patients with billowing mitral valve leaflets.*

DR. MARTIN M. LEWINTER:* The diagnosis of mitral valve prolapse generally can be made by the presence of the typical auscultatory findings or mitral valve echocardiographic patterns described above, or both. Therefore, at present cardiac catheterization and left ventriculography are usually unnecessary to establish the diagnosis of mitral valve prolapse. Those patients in whom cardiac catherization is indicated generally fall into three groups: patients with chest pain in whom it is desirable to rule out the presence of coronary artery disease, patients who have clinical findings suggesting hemodynamically significant mitral regurgitation, and patients in whom some associated condition—such as atrial septal defect or hypertrophic cardiomyopathy—is suspected. As a cor-

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ollary, the recent literature describing hemodynamic and angiographic data in patients with this syndrome concerns more symptomatic patients and is probably not representative of the majority of patients with prolapsing mitral valve leaflets.

Most patients with a midsystolic click, late systolic murmur, or both, have normal resting intracardiac pressures at catheterization unless an associated cardiac abnormality is present. Barlow et al[23] reported that in 20 of 21 patients with this syndrome there were normal left ventricular pressures, the exception being a patient with associated hypertrophic cardiomyopathy. The left atrial pressure was normal in all seven patients in whom it was measured and in nine out of ten there were normal right heart pressures; there was an associated atrial septal defect in the one exception. Occasionally, in a patient with this syndrome there will be a mildly elevated left ventricular end-diastolic pressure[58,59] or an increase in the pulmonary artery wedge pressure associated with a prominent "v" wave on exercise.[10] Jeresaty[58] noted an exaggerated early diastolic dip followed by a rapid rise to a mid-diastolic plateau (square-root sign) in the right ventricular pressure recordings of two patients, in the left ventricular tracings of two other patients and in both right and left ventricular pressure tracings in one patient with this syndrome, this finding is similar to that seen in patients with restrictive pericardial or myocardial disease.

Patients with longer systolic murmurs or holosystolic murmurs tend to have more significant grades of mitral regurgitation.[60,61] In these persons, the hemodynamic findings are essentially identical to those with mitral regurgitation of other causes. Thus, variable degrees of elevation of the left ventricular end-diastolic pressure and pulmonary hypertension will be found and the "v" wave of the pulmonary artery wedge or directly obtained left atrial pressure may be prominent. In this group of patients the cardiac index may be depressed if mitral regurgitation is severe.

For descriptive purposes the angiographic find-

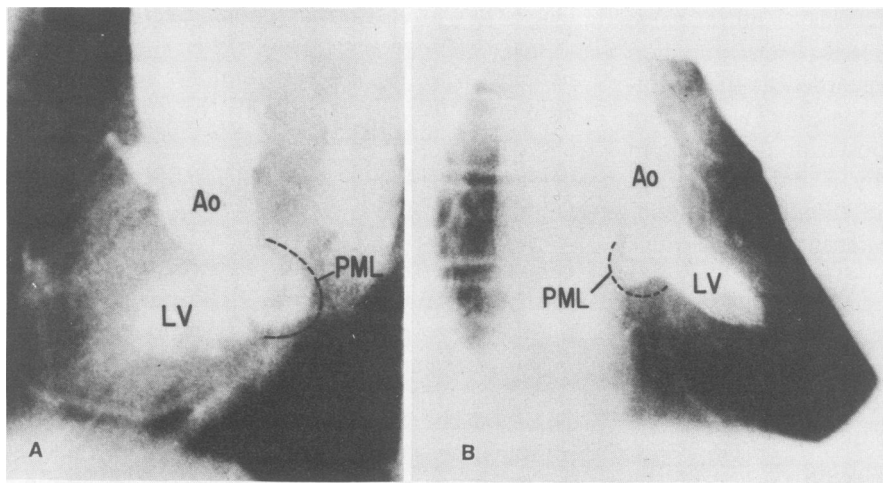

Figure 6.—Systolic frames from a left ventricular cineangiogram in the lateral **(A)** and anteroposterior **(B)** views showing prolapse of the posterior mitral valve leaflet (PML). LV=left ventricle; Ao=aorta.

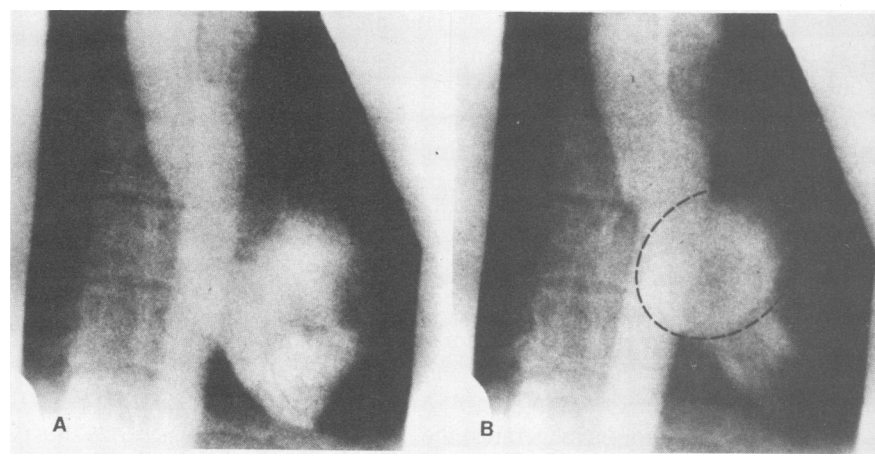

Figure 7.—End-diastolic **(A)** and end-systolic **(B)** frames of a left ventricular cineangiogram in the anteroposterior projection illustrating pronounced systolic prolapse of both leaflets and a "doughnut" deformity of the mitral valve (see text).

ings in patients with mitral valve prolapse can conveniently be divided into those due to the prolapsed mitral leaflets themselves and those relating to contraction abnormalities of the left ventricle. However, what relationship the two abnormalities have constitutes an important unsolved problem in patients with this syndrome.

Earlier angiographic studies were primarily concerned with documenting the presence of prolapse of the mitral valve leaflets into the left atrium during systole and correlating this observation with the auscultatory findings. In Barlow's original and expanded series of patients,[23,60] prolapse of the posterior leaflet was emphasized with little attention directed to anterior leaflet involvement. Patients with a midsystolic or late systolic click and no systolic murmur, often had no demonstrable mitral regurgitation.

Subsequent studies have further characterized and refined our understanding of the mitral valve abnormality. Linhart[58] and Jeresaty[62] emphasized the frequency of anterior leaflet involvement in addition to the posterior leaflet, while Bittar and Sosa[61] studied three patients in whom mitral regurgitation was so severe that valve replacement was required.

Typical examples of mitral leaflet prolapse from our laboratory are represented in Figures 6, 7 and 8. Figure 6 shows discrete prolapse of the posterior leaflet into the left atrium during systole. Of interest is the fact that this patient was admitted to the hospital with chest pain and a diagnosis of "crescendo angina." The heart sounds were distant and the diagnosis of prolapse was not suspected at the bedside. Findings on selective coronary arteriograms were normal in this patient. Figures 7 and 8 show notably reduplicated or "floppy" valves, with pronounced prolapse—probably of both leaflets—into the left atrium. In our experience this gross malformation of the mitral leaflets is present in a minority of patients.

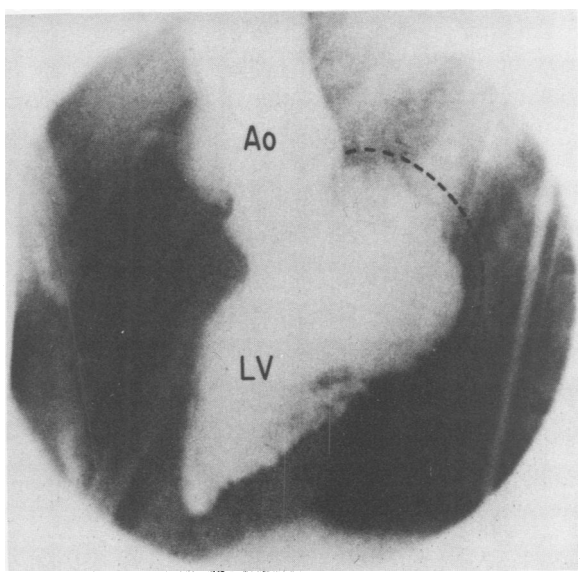

Figure 8.—A systolic left ventricular cine frame in the lateral projection showing severe prolapse of the mitral valve leaflets into the left atrium.

Ranganathan et al[63] have studied the morphology of the posterior mitral valve leaflet in postmortem specimens and in most cases found that it was a triscalloped structure; usually there was a large middle scallop surrounded by smaller anterolateral and posteromedial scallops. Using these morphologic findings, these authors[64] and Jeresaty[65] have attempted to refine further the angiographic interpretation of mitral valve prolapse with respect to the precise identification of which scallop or scallops of the posterior leaflet are involved and whether or not anterior leaflet prolapse is also present. According to the authors, the example shown in Figure 6 would most likely represent prolapse of the posteromedial and middle scallop of the posterior leaflet.

Another well-recognized angiographic pattern (Figure 7) is a doughnut-shaped mitral valve which is felt to represent generalized prolapse of both leaflets.

While Leachman[66] and Criley[8] identified abnormal systolic expansion of the mitral annulus in patients with mitral valve prolapse, Ehlers and associates[67] were the first to recognize contraction abnormalities of the left ventricle in association with the condition. Left ventriculography was done by these authors in a group of six females between the ages of 12 and 24—in all of whom there were typical auscultatory findings—and noted in each that the posteroinferior aspect of the left ventricle bulged into the cavity during systole producing, in the frontal projection, the appearance of a contraction ring. Subsequently, Liedtke and coworkers[44] analyzed mean circumferential fiber shortening rates in patients with prolapse at the proximal, middle and apical portions of the left ventricle and found significant reductions at the proximal level, near the mitral valve. Scampardonis et al[43] analyzed a large number of patients with prolapse and were able to identify five classes of abnormal left ventricular contraction patterns. These included posterior wall akinesis, decreased long axis shortening, an

inferior convexity with an anterior bulge (the ballerina foot), a contraction ring (the hourglass deformity), and left ventricular cavity obliteration. Finally, Gulotta et al[46] noted varying degrees of hypokinesis or dyskinesis (systolic bulging) of the anterolateral left ventricular wall in 20 of 22 patients undergoing left ventriculography. Schematic representations of some of these abnormal left ventricular contraction patterns are shown in Figure 9.

Thus, the spectrum of contraction abnormalities seen in patients with mital valve prolapse varies from subtle areas of diminished contractility to frank dyskinesis. Most of these contraction abnormalities are well localized and display a close anatomic and functional relationship to the mitral valve apparatus. What percentage of patients with prolapse exhibit such contraction abnormalities is not known at present, but several investigators have been sufficiently impressed with the frequency of angiographic abnormalities to suggest that the major problem in this group of patients may be a rather unusual segmental cardiomyopathy affecting the mitral valve apparatus and secondarily allowing prolapse. Since, in addition, there are many patients without angiographically detectable contraction abnormalities, it may ultimately become necessary to divide patients with mitral valve prolapse into a primary and secondary group, the latter containing those *with* contraction abnormalities affecting the valve apparatus. Clearly, this is an area which requires further careful study.

In 1973, Jeresaty[62] reviewed the available literature concerning coronary arteriograms in patients with the billowing leaflet syndrome. Findings on the coronary angiograms were normal in 118, mildly abnormal in two and significantly abnormal in two reported patients with mitral leaflet prolapse, excluding Cheng's series[68] which Jeresaty felt represented examples of coronary artery disease with papillary muscle dysfunction. In our experience also the findings on coronary arteriograms are usually normal in patients with billowing mitral leaflets. As indicated by Dr. Johnson, the occasional patient with mitral prolapse and coronary artery heart disease may represent the chance coexistence of two common entities. The available evidence would suggest that occlusive disease of the coronary arteries does not represent a part of the prolapsing mitral leaflet syndrome.

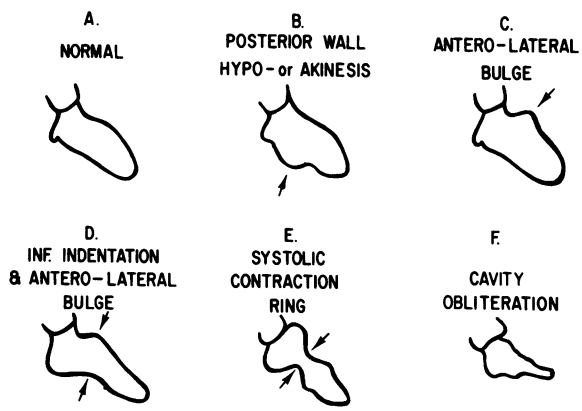

Figure 9.—A composite representation of several left ventricular contraction abnormalities described in association with mitral valve prolapse. Systolic frames from left ventriculograms obtained in the right anterior oblique projection are depicted.

A number of workers[10,29,69] have commented on the association of mitral valve prolapse with secundum atrial septal defect. Conversely, it has been suggested that 10 to 15 percent of patients with secundum atrial septal defect may have prolapsing mitral valve leaflets.[70] If this is the case, then the presence of a secundum atrial septal defect is an indication for at least a mitral valve echocardiogram in order to make a judgment with regard to endocarditis prophylaxis (mentioned later). Conversely, any suggestion of the presence of an atrial septal defect in a patient with prolapse necessitates ruling out a left to right shunt and may be viewed as an indication for right heart catheterization.

Another possibly associated condition which may be documented at cardiac catheterization is that of hypertrophic cardiomyopathy. There have been isolated case reports of this association in the literature[23] and Scampardonis[43] recognized a group of patients with angiographic evidence of left ventricular cavity obliteration during systole. What significance this apparent association has is not clear at present.

Finally, mention must be made of tricuspid valve leaflet prolapse in association with mitral valve prolapse, a surprisingly high incidence of which was noted by Scampardonis[43] in his series of patients undergoing both left and right ventriculography. This finding requires further verification by others.

DR. O'ROURKE: *The mitral regurgitation in patients with the prolapsing mitral valve leaflet syndrome is usually mild and does not warrant mitral*

valve replacement. However, the incidence of progression to severe mitral regurgitation and the occurrence rate of ruptured chordae tendinae remain unknown.

The treatment of patients with mitral valve prolapse is directed toward the prevention of bacterial endocarditis, the relief of atypical chest pain and the prevention of cardiac arrhythmias. Dr. Karliner will discuss the role of medical therapy in patients with this syndrome.

DR. JOEL S. KARLINER:* Many patients with the prolapsing mitral valve leaflet syndrome report chest discomfort that sometimes resembles angina pectoris. More often, however, the precordial pain is atypical in nature; it tends to be prolonged, inconsistently related to exertion and only occasionally relieved by nitroglycerin. Coronary arteriograms in such patients usually have not shown significant occlusive disease.[40,46] The origin of the atypical chest pain is obscure. In addition to atherosclerotic heart disease,[26] it has been ascribed to compression of the left circumflex coronary artery,[23,71] interference with the papillary muscle blood supply[27] and psychological factors.[10] As mentioned by Dr. Crawford, our own data indicate that an imbalance between myocardial oxygen supply and demand may play an important role in the pathogenesis of symptoms in these patients.[21]

Because of the resemblance of the chest pain to the discomfort experienced by patients with ischemic heart disease and the possibility that the pain may be related to alterations in myocardial oxygen demand, beta-adrenergic blockade has been used by a number of investigators with varying success. Sloman and his colleagues reported that propranolol (120 mg daily) controlled the pain in three and produced improvement in two patients, but caused no relief in three other patients.[72] Others have proposed that propranolol should be used in the treatment of atypical chest pain in patients with this syndrome,[71,73] and our own experience has indicated that the incidence and severity of precordial discomfort may be lessened or sometimes even abolished by propranolol therapy. However, in patients with hemodynamically and angiographically documented left ventricular dysfunction, propranolol may be ineffective in producing relief of symptoms.[46] Nevertheless, in patients who have atypical chest pain as a major complaint, the use of oral propranolol in a dose sufficient to produce adequate beta-adrenergic blockade (resting heart of less than 55 to 60 beats per minute) should be considered. It must be emphasized, however, that there are no published controlled studies of propranolol (or any other mode of therapy) in the treatment of chest pain accompanying this disorder, and that the favorable results reported are based largely upon subjective appraisals.

It is well known that life threatening arrhythmias may occur in patients with mitral valve prolapse. The precise incidence of these arrhythmias is uncertain, but they tend to be more common, as does sudden death, where there is a family history of the syndrome[29] or with patients in whom there is abnormal left ventricular wall motion.[40] Thus, Pocock and Barlow have advocated exercise testing of all patients with billowing mitral leaflets, since serious ventricular arrhythmias may be unmasked by this maneuver.[20] Of considerable interest is the high incidence of QT interval prolongation reported by several authors in patients without a family history of syncope or hereditary deafness.[10,40] In one remarkable patient with ballooning mitral leaflets and a prolonged QT interval who recovered from an initial bout of ventricular fibrillation but who died suddenly after hospital discharge, the coronary arteries and the conduction system were both grossly and microscopically normal.[19] Because of QT interval prolongation, propranolol and diphenylhydantoin—both of which tend to shorten the QT interval—were used to treat arrhythmias in these patients but without success. Pocock and Barlow successfully treated three patients with exercise-induced multifocal ventricular arrhythmias, one with diphenylhydantoin and two with propranolol.[20] Conversely, Gooch and his colleagues reported that none of four agents (digitalis, quinidine, propranolol and procainamide) was completely effective in abolishing exercise-induced arrhythmias in several patients.[40] Of considerable interest is the report of Gulotta and associates who observed two patients with mitral valve prolapse who developed complete heart block requiring permanent transvenous pacemaker implantation.[46]

The cause of the prolonged QT interval and the propensity to arrhythmias in these patients has not been adequately explained. It has been proposed that QT interval prolongation may be associated with unilateral autonomic imbalance

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(excess sympathetic tone) resulting in nonhomogeneous ventricular repolarization.[74] An intriguing possibility, as yet quite speculative, is that such autonomic imbalance may be related to the high incidence of psychiatric disorders observed in this syndrome. Indeed, Shapell and Gunn have reported that in four of six patients with billowing mitral leaflets and abnormal findings on a Minnesota Multi-Phasic Personality Inventory, serious ventricular arrhythmias occurred, including two episodes requiring cardiopulmonary resuscitation.[75]

Therefore, it is our policy that all patients with the "click-murmur" syndrome undergo exercise stress-testing, even though the incidence of serious arrhythmias unmasked by such a procedure may be low.[76] Furthermore, prolonged ambulatory ECG monitoring is recommended in all patients who complain of palpitations. Should serious arrhythmias be found, therapy with propranolol or other antiarrhythmic agents appears warranted. Under such circumstances, routine follow-up studies using both ambulatory ECG monitoring and exercise studies, are indicated.

A number of instances of bacterial endocarditis have been reported in patients with mitral valve prolapse, most of which have been due to streptococcus virdans.[14,29,52,72,77-79] Patients in whom there is a systolic click only and no murmur are not spared this complication.[80] In view of the clear association between bacterial endocarditis—especially the variety caused by streptococcus virdans—and billowing mitral leaflets, appropriate endocarditis antibiotic prophylaxis appears to be indicated for dental and surgical procedures in patients with this syndrome.

DR. O'ROURKE: In concluding this specialty conference I should like to emphasize that the prolapsing mitral valve leaflet syndrome is a common entity with protean manifestations including systolic murmurs, systolic clicks, atypical chest pain, abnormal resting electrocardiograms and resting or exercise-induced arrhythmias. Any combination or none of the clinical features may be associated with echocardiographic or angiocardiographic evidence of mitral valve prolapse.

The current definition of this syndrome most likely applies to several subsets of patients who differ in regard to the causes, pathogenesis and hemodynamic sequelae of their abnormal mitral valve function. Careful epidemiologic, clinical follow-up, hemodynamic and pathologic studies should improve our understanding of this common but complex clinical syndrome.

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